Journal of the Formosan Medical Association (2013) 112, 283–286

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CASE REPORT

Madelung's disease associated with polyneuropathy and symptomatic hypokalemia

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Received 29 October 2009; received in revised form 20 January 2010; accepted 10 March 2010

KEYWORDS
hypokalemic periodic paralysis;
Launois–Bensaude syndrome;
Madelung's disease;
multiple symmetric lipomatosis;
polyneuropathy

Madelung's disease (multiple symmetric lipomatosis) is a rare disease characterized by abnormal diffuse lipomatosis in proximal upper limbs and neck. Previous reports have shown that this disease is associated with alcoholism, polyneuropathy, mitochondrial disease, and glucose intolerance. Here, we describe a 46-year-old man having Madelung's disease associated with polyneuropathy and symptomatic hypokalemia. He presented with insidious-onset weakness and numbness in lower limbs for 7 years and recent deterioration of symptoms. Proximal weakness improved with potassium supplement. Our observation may extend the phenotype of Madelung's disease to hypokalemic periodic paralysis.

Introduction

Madelung's disease, also called multiple symmetric lipomatosis (MSL), is a rare disease and characterized by abnormal diffuse lipomas located in the neck, shoulder, and inguinal areas. Patients often seek medical help for cosmetic reason. Most of the patients are alcoholic.[1–3] There are occasional associations with polyneuropathy, mitochondrial disease, and glucose intolerance.[4–6] The pathophysiology of MSL is uncertain, but defect in lipolytic pathway and mitochondrial defect are reported.[1,4,6,7] Here, we present a case of MSL with multiple neurological manifestations.

Case report

A 46-year-old man presented with a history of alcoholism for 10 years (about 500–800 mL of 40% alcohol beverage per day). Insidious onset of mild distal predominant numbness and weakness on the four limbs were noted about 7 years ago, without affecting his daily life very much in the initial years. Although he had a habit of alcohol consumption, he claimed to have regular diet every day. He found symmetric, gradually enlarging, painless soft mass developing around his neck, shoulders, proximal upper limbs, and inguinal areas since 4 years ago. He had even asked for help in a local hospital, but no definite diagnosis was made

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0929-6646/$ - see front matter
http://dx.doi.org/10.1016/j.jfma.2012.07.019

there. The patient did not receive any treatment until 3 days before admission. He visited our outpatient clinic for progressive worsening of proximal weakness since the last 3 days before admission, which made him unable to climb stairs without assistance. He needed to perform some warm-up exercise for getting up from squatting position. He did not have a large amount of carbohydrate intake or exercise recently. There was no urinary retention, but erectile dysfunction was noted in recent months. Physical examination revealed normal blood pressure (120/90 mmHg) and normal body temperature (36.5°C). Multiple painless, movable masses, without margin, erythematous change, or induration, were seen around neck, shoulder, and proximal upper limbs (Fig. 1). Neurological examination showed proximal weakness with increased knee jerk on the lower limb and abdominal rectus without pathological reflex. Ascending hypesthesia and reduced vibration sensation from toes up to knee were noted.

Laboratory work-up showed anemia with upper limit mean corpuscular volume (MCV: 95.5 fL; Hb: 11.4 g/dL), hypokalemia (2.5 meq/L), reduced folic acid level (5.17 ng/mL), normal thyroid function test (T3: 93.95 ng/dL; TSH 2.0491 mIU/L), and normal Vit B12 level (189 ng/mL). Further work-up for hypokalemia, including transtubular potassium gradient 2.57 (normal <3), urine potassium 7.4 mEq/L (normal <20 mEq/L), and urine chloride 148 mEq/L (normal >20 mEq/L), indicated that there was no renal loss of potassium. Muscle enzyme, lipid profile, and renal function were all within normal limit. Electrophysiological study showed sensorimotor polyneuropathy with mild slowing of motor nerve conduction velocity. Sympathetic skin response and R—R interval variation test were performed for suspected autonomic dysfunction, but the results were within normal limit. Electromyography showed no myopathic change. Somatosensory evoked potential showed prolonged central conduction time and suggested possible cervical myelopathy, but spine MRI showed mild cervical stenosis without significant cord compression. Neck CT showed diffuse lipomatosis around neck and upper back along both muscular and fascia planes, which is different from the findings in common obesity (Fig. 2). Carotid duplex study showed no significant stenosis on the extracranial cervical arteries. Study on the mitochondrial gene mutation (MERRF, myoclonic epilepsy with ragged red fibers, A8344G) was negative. Besides, we arranged a prolonged exercise test, which induced the decrease of compound motor action potential on the femoral nerve. Proximal weakness improved with potassium supplements. Considering his proximal weakness with warm-up phenomenon, hypokalemia with the positive result of prolonged exercise,[8] and good response to potassium supplement, periodic paralysis is possible. He possibly also had mild cervical myelopathy, as suggested by increased deep tendon reflex of lower limbs and prolonged central conduction time on somatosensory evoked potential despite no significant cord compression on MRI. Folic acid deficiency-related myelopathy was also considered. Based on his multiple lipomatosis, and neck CT reports in combination with the aforementioned examinations, we diagnosed this case as Madelung's disease (MSL) with mild sensorimotor polyneuropathy, myelopathy, and possible periodic paralysis.

Figure 1 Photograph of a patient, showing lipoma around the neck, shoulders, and arms (arrows).

Discussion

MSL is a rare syndrome of large confluent symmetric lipomas around the neck, shoulder, or trunk. Benjamine Brodie first described this disease in St George hospital in 1846.[4] In addition to Madelung's disease and MSL, it was also named as Launois—Bensaude syndrome.[5] By performing a literature review using PubMed, only about 250 cases were found to be reported since 1954 to 2009. It is more common in the Mediterranean region, and its incidence was reported as 1/25,000 in Italian population.[9] Only a few cases were reported in Asia.[1,10] The diagnosis of MSL is based on a "sight diagnosis" by demonstrating multiple, symmetric fatty accumulations typically distribution in the neck and proximal upper trunk; the rest of body does not show much fatty accumulations. This distribution is different from that in case of simple obesity, which generally has fat tissues on the four limbs and trunk. Besides, image of fatty accumulations shows that the fatty bulk in MSL is noncapsulated and distributed along vascular and muscular planes, in contrast with lipoma, which is capsulated in subcutaneous space. Most patients are associated with alcoholism, but the casual effect between alcohol and MSL is unknown.[1,2,4,5] Alcoholism-related macrocytic anemia and elevated liver enzyme are noted. Axonal predominant polyneuropathy and autonomic dysfunction are common neurological complications.[1,3—5,11] Whether all the aforementioned neurological manifestations are directly related to MSL or they are the results of alcoholism still remains controversial. In some reports, occurrence of polyneuropathy was attributed to chronic alcohol consumption.[4] Occasional comorbidity associated with diabetes mellitus, hyperuricemia, hyperalphalipoproteinemia, and thyroid disorder was reported.[1]

Etiology of this disease is still unclear. At first, an abnormal lipolytic process in response to catecholamine-inducing lipid mobilization was proposed.[1,4] Recently, there were serial reports suggesting the relationship between MSL

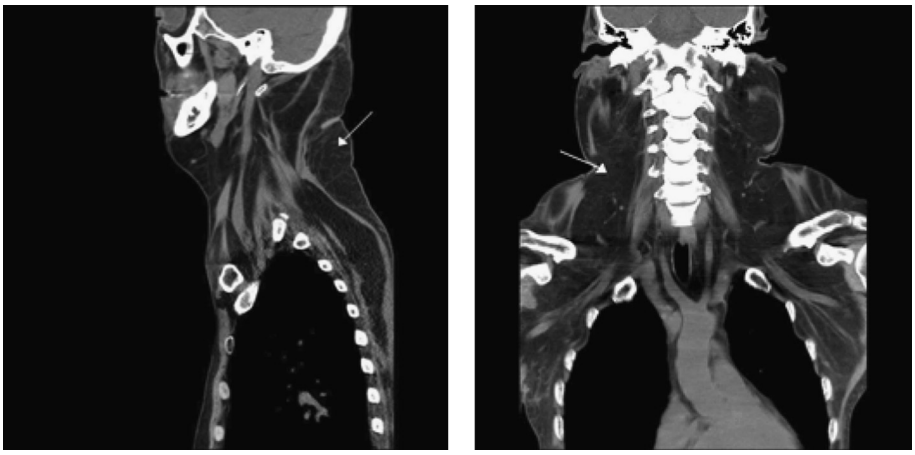

Figure 2 Neck MRI showing fat tissue distribution around the cervical and thoracic spine and shoulder inside the muscular and vascular planes (arrows).

and mitochondrial disease such as MERRF in some patients.[6,7,12,13] However, these patients with both lipolytic and mitochondrial diseases had additional symptoms suggesting mitochondrial cytopathy, such as ataxia, myoclonus, myopathy, or neuropathy, which were not shown in other reports on MSL. Furthermore, no mitochondrial disorder was reported in several studies of familial MSL.[14,15] Our patient had no mutation of MERRF or other sign of mitochondrial disease. It suggested the heterogeneity of different pathogenesis process in MSL.

Treatment is indicated mainly for cosmetic reason, including liposuction and direct lipoectomy. In rare cases with lipomatosis extending to mediastinum and tracheal compression, tracheostomy was needed.[3] Diet control with low intake of fat could not arrest the progression of lipomatosis.[16] Abstinence from alcohol may reduce or even stop the progression of lipomatosis.[3] Enzi et al followed up 31 MSL patients for 4—26 years, with mortality being as high as 25%. Out of the eight patients who died, nearly half (three patients) had sudden death and all had autonomic neuropathy and no coronary heart disease.[3] Overall, long-term follow-up reports are still limited.

In past decades, only two patients with MSL were reported in Taiwan, who had no polyneuropathy or other neurologic symptom.[10] We presented a case of MSL associated with alcoholism, polyneuropathy, symptomatic hypokalemia, and possible myelopathy. His past history of long-term alcohol consumption and evidence of polyneuropathy are the same to previous reported comorbidity. In addition, our patient presented with symptoms of hypokalemic periodic paralysis, which was not due to thyroid disease or poor dietary intake. However, overactivation of hypothalamic—pituitary—adrenal axis in alcoholism can also cause hypertensive hypokalemia,[17] which was not the case in our patient (extrarenal loss of potassium). This is the first report of a case with a possible comorbidity of hypokalemic periodic paralysis in MSL patients.

Conclusion

Our case report may extend the phenotype of MSL with symptomatic hypokalemia. MSL patients with episodic attack of paralysis need further care in medical management.

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